



REMARKS

Claims 1-19, 29-32 and 36-42 are pending in the instant applications. Claims 1-11, 13 and 16 have been rejected. Claims 1-16 have been objected to. Claim 9 has been cancelled. Claims 1-8 and 10-16 have been amended to remove non-elected subject matter. These amendments do not introduce any new subject matter, and support for them can be found in the specification. Claims 17-19, 29-32, and 36-42 have been cancelled as they are drawn to non-elected subject matter. After entry of this amendment, Claims 1-8 and 10-16 will be pending.

Specification

The Examiner states that the application does not contain an abstract of disclosure. Applicants believe that an abstract was included in the original filing, however, an abstract has been added to the specification.

Information Disclosure Statement

The Examiner states that the reference by Iwasawa et. al. was not considered because a copy was not provided. Applicants respectfully maintain that a copy of this article was included in the IDS submitted on July 25, 2007. However, Applicants have included a copy of the Iwasawa et. al. paper. Therefore, the Applicants respectfully request that the Examiner consider the reference.

Additionally, the Examiner states that the reference by Ranjon et. al. was not considered because an English translation was not provided. Applicants respectfully request that the Examiner consider the reference, as the Applicants have provided an Explanation of Relevance of Non-English Documents as provided by 37 C.F.R. 1.98(a)(3)(i), which was submitted on July 25, 2005.

Objections to Claims 1-16

The Examiner has objected to claims 1-16 for containing non-elected subject matter. Applicants have amended the instant claims to remove the non-elected subject matter. In light of these amendments, this objection should be rendered moot. According, Applicants respectfully request the objection of Claims 1-16, be withdrawn.

Rejection of Claims 1-10 and 16 under 35 USC §112, first paragraph

The Examiner has rejected Claims 1-10 and 16 under 35 U.S.C §112, first paragraph for allegedly failing to comply with the written description requirement. Specifically the Examiner stated that:

To fulfill the written description requirement, a patent specification must describe and invention...in sufficient detail that one skilled in the art can clearly conclude that 'the inventor invented the claimed invention' *Lockwood v. American Airlines, Inc.*, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

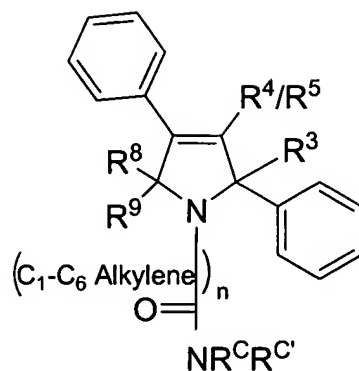
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The MPEP states that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species...to reflect the variation within that genus (MPEP 2163). The written description requirement may be satisfied through a sufficient description of a representative number of species by (a) actual reduction to practice, (b) reduction to drawings or structural chemical formulas; (c) disclosure of relevant, identifying characteristics by functional characteristics coupled with known or disclosed correlations between function and structure.

The Examiner asserts that substantial structural variation exists in the genus/subgenus embraced by claims 1-10 and 16. The disclosure of species supporting the genus/subgenus is limited to compounds reduced to practice, which is not commensurate in scope with the genus/subgenus claimed. Accordingly, it is deemed that the specification allegedly fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor at the time the application was filed had possession of the entire scope of the invention. The Examiner produced the analysis below, which compares the scope of the claim and the scope of the description to determine whether Applicants demonstrated possession of the invention:

I. Scope of the Claims:

Claims 1-10, 16: Compounds of Formula Scheme 1 (see structure below), salt stereoisomer, or pharmaceutical composition thereof;



Scheme 1

Where variables are defined as the following:

R¹ = (C₁-C₆ alkylene)_n(C=O)N R^CR^{C'}, optionally substituted

R² = R⁶ = optionally substituted phenyl

R³ = R⁴/R⁵ = R⁸ = R⁹ = H or unsubstituted C₁-C₁₀ alkyl

II. Scope of the Disclosure:

Reduction to Practice: compounds representing the following substituents

R³, R⁴/R⁵, R⁸, R⁹: H or C₁-C₁₀ alkyl (unsubstituted)

R¹⁰: Halogen, alkyl (optionally substituted with a halogen), CN, OH

R^C and R^{C'}: Alkyl optionally substituted with the following:

OH, -CO₂H, alkoxy

(C=O)morpholine (optionally substituted alkyl)

O(C=O)-piperazine or piperidine or morpholine

Phenyl, pyridine

Ozazole, pyrazole, oxadiazole, thiazole, triazole

Oxopyridine, oxotriazole

Piperidine, piperazine

Tetrahydrofuran, dioxolane, dioxane

R^C and R^{C'}: together form morpholine, azetidine, pyrrolidine

Note: All variables optionally substituted with halogen or alkyl

Without conceding the correctness of the Examiner's argument, but to advance the prosecution of the instant application, Applicants have cancelled Claim 9. In light of this cancellation, the rejection of Claim 9 should be rendered moot.

However, Applicants respectfully traverse rejection of Claims 1-8, 10 and 16.

For a written description rejection, the Examiner has the "initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure of the invention defined by the claims." MPEP 2163.04 (citing *In re Wertheim*, 191 USPQ 90, 97(1976)). For Claims 1-8, 10 and 16, the Examiner has not met this initial burden of establishing a reasonable basis for questioning Applicants completion of the written description requirement.

In the instant case, the Examiner contends that Applicants reduced to practice a limited number compounds in Claims 1-10 and 16, which was not a sufficient representation of the large number of compounds encompassed by the claims. In particular, the Examiner asserted that the substituents R^3 , R^4/R^5 , R^8 , R^9 , and R^{10} were not adequately represented by the specification.

Applicants respectfully contend that the examples provided in the specification adequately describe all of the aforementioned substituents in the claims.

The Examiner states that Applicants merely reduced to practice four examples of a R^{10} substitution, namely a halogen, alkyl, cyano, and hydroxy group. However, Applicants respectfully maintain that the examples section of the specification illustrates at least eleven embodiments of R^{10} substitutions. Representative examples are illustrated below (please note that the list of examples are not exhaustive):

1. $(C=O)_aO_bC_{1-C_{10}}$ alkyl: Exemplified by Compounds 2-10 and 4-7 (pg. 143, 149) - Methyl substituted on R^6 and Methyl substituted on R^2 , respectively
2. $(C=O)_aO_b$ aryl: Exemplified by Compound 19-4 (pg. 204) - Phenyl substituted on R^C/R^C
3. C_2-C_{10} alkenyl: Exemplified by Compound 18-13 (pg. 201) – Allyl substituted on R^C/R^C
4. $(C=O)_aO_b$ heterocyclyl: Exemplified by Compounds 18-10 and 18-11 (pg. 201) - Pyrrolidinyl and dioxolanyl, respectively, substituted on R^C/R^C

5. CO₂H: Exemplified by Compound 35-4 (pg. 275) – carbonyl substituted on R^C/R^{C'}
6. Halogen: Exemplified by Compound 1-6 (pg. 136) - F and Cl substituted on R⁶
7. CN: Exemplified by Compounds 13-1 (pg. 163) - CN substituted on R⁶
8. OH: Exemplified by Compounds 19-7 and 35-2 (pg. 205, 273) - OH substituted on R^C/R^{C'} and OH substituted on R², respectively
9. O_bC₁-C₆ perfluoroalkyl: Exemplified by Compound 3-2 (pg. 145) – CF₃ on R⁶
10. O_a(C=O)_bNR¹²R¹³: Exemplified by Compounds 19-6 (pg. 205) – Amino groups substituted on R^C/R^{C'}
11. (S=O)_mR^a: Exemplified by Compound 35-42 (pg. 287) – Sulfonyl group substituted on R^C/R^{C'}

Additionally, the Examiner claimed that the Applicants only reduced to practice two examples of R^C/R^{C'} substituents, namely a substituted alkyl and R^C/R^{C'} joining to form a heterocycle. However, Applicants respectfully maintain that the specification is enabling for each of the R^C/R^{C'} substituents. Representative examples are illustrated below (please note that the list of examples is not exhaustive):

1. H: Exemplified by Compound 19-13 (pg. 206)
2. C₁-C₁₀ alkyl: Exemplified by Compound 1-6 (pg. 136)
3. heterocycle: Exemplified by Compounds 18-5 thru 18-8 (pg. 200)
4. (C₃-C₆)cycloalkyl: Exemplified by Compounds 28-12 (pg. 244)
5. R^C/R^{C'} together with the nitrogen to form a heterocycle: Exemplified by Compound 2-12 (pg. 143) –R^C and R^{C'} combine to form a morpholine

The Applicants also maintain that adequate support exists in the specification for all of the substituents including, but not limited to R³, R⁴/R⁵, R⁸, R⁹, R¹¹ and R¹²/R¹³.

For example, as a result of the species elected by the Applicants, R³, R⁴/R⁵, R⁸, and R⁹ can only be hydrogen or an unsubstituted C₁-C₁₀ alkyl. Additionally, Claim 1 provides

20 possible substituents for R¹¹, 10 of which are described in the specification either as a compound that has been actually reduced to practice (pg. pg. 145, 201, 202, 204, 278, 283, 297, 298) or listed as a preferred substitution (pg. 91). Similarly, Claim 1 provides 13 possible substituents for R¹²/R¹³, three of which are shown as examples in the specification (pg. 149, 205, 281).

According to the MPEP, the written description requirement for a claimed genus may be satisfied through a sufficient description of a representative number of species (2163.05). If the genus contains substantial variation, the Applicant must "describe a sufficient variety of species to reflect the variation within the genus" (MPEP 2163.05). Although the MPEP does not specify what constitutes a "representative number of species", typically more than one embodiment is required to satisfy the written description requirement. In the instant application, Applicants have provided a significantly more than the requisite number of embodiments to ensure that the variation within the species is reflected.

Applicants maintain that the Examiner has not made a prima facie case of lack of written description, and in light of the arguments presented, it is not reasonable to conclude that Applicants have not sufficiently described the claims. Accordingly, Applicants respectfully request the rejection of Claims 3, 4, and 7 under 35 U.S.C. §112, first paragraph, be withdrawn.

Enablement

The Examiner has also rejected claims 1-10 and 16 under 35 U.S.C. §112, first paragraph, for allegedly containing subject matter which was not described in the specification in a manner to enable one skilled in the art to make and/or use the invention. Specifically the Examiner stated that:

The specification does not enable any person skilled in the art to which it pertains...to practice the invention commensurate in scope with these claims. The standard for determining whether the specification meets the enablement requirement...is [whether] the experimentation needed to practice the invention is undue or unreasonable? *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916).

The MPEP states that there are many factors to be considered when determining whether the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue. The factors to be considered are the (1) breadth of the claim, (2)

nature of invention, (3) state of prior art, (4) level of ordinary skill, (5) level of predictability, (6) amount of direction provided by the inventor, (7) existence of working examples, and (8) quantity of experimentation needed to make or use the invention (MPEP 2164.01(a)).

In the instant application, the Examiner alleges that due to the low level of predictability in the art, absent guidance, one of ordinary skill would not expect that all of the compounds encompassed by the genus would have activity. Since one of ordinary skill would not know which compounds not exemplified would possess the claimed activity, a skilled artisan would be subject to undue experimentation to determine which compounds in the broad genus claimed would have activity required to practice the invention.

Without conceding the correctness of the Examiner's argument, but to advance the prosecution of the instant application, applicants have cancelled Claim 9. In light of this cancellation, the rejection of Claim 9 should be rendered moot.

However, Applicants respectfully traverse the rejection of Claims 1-8, 10 and 16.

In order to make a rejection based upon lack of enablement, the Examiner has the initial burden to explain why the scope of protection provided by a claim is not adequately enabled by the disclosure (MPEP 2164.04). The specification disclosure which contains a teaching of the manner and process of making and using the invention...must be taken as being in compliance with the enablement requirement...unless there is a reason to doubt the objective truth of the statement (MPEP 2164.04). In the instant application, the Examiner states that due to the low level of predictability in the art, a person skilled in the art would be subjected to undue experimentation to determine which compound would possess activity. The Applicants disagree with the Examiner's allegation.

The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation (MPEP 2164.01). "An extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." *In re Colianni*, 195 USPQ 150, 153 (1977). "[A] considerable amount of experimentation is permissible...if the specification in question provides a reasonable amount to guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 8 USPQ2d 1400, 1404 (1988). In the instant case, Applicants have provided 9 generic schemes that can be used for guidance in making compounds of the present invention (pg. 96-102) and included detailed instructions of how to synthesize 420 compounds that were reduced to practice (pg. 136-305). According to the MPEP, as long as the specification discloses *at least*

one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement is satisfied (MPEP 2164.01(b), emphasis added). These examples clearly provide guidance to one skilled in the art how to proceed with further experimentation. One skilled in the art, after reading the disclosure would not have to engage in undue experimentation

Applicants maintain that the Examiner has not made a prima facie case of nonenablement, and in light of the argument presented, it is not reasonable to conclude that the Applicant has not enabled the claims. Accordingly, Applicants respectfully request the rejection of Claims 1-10 and 16 under 35 U.S.C. §112, first paragraph, be withdrawn.

Rejection of Claims 1-10 and 16 under 35 USC §112, second paragraph

The Examiner rejected Claims 1-10 and 16 under 35 U.S.C. 112, second paragraph for being indefinite and failing to point out and distinctly claim the subject matter the applicant regards as the invention. Specifically, the Examiner indicated that the 14th and 16th option for R¹⁰ in the claims would violate the valence requirement. Without conceding the correctness of the Examiner's argument, but to advance the prosecution of the instant application, Applicants have amended Claim 1-10 and 16 to remove Option 14 and 16 under R¹⁰. In light of these amendments, this rejection should be rendered moot. Accordingly, Applicants respectfully request the rejection of claims 1-10 and 16 under 35 U.S.C. §112, second paragraph, be withdrawn.

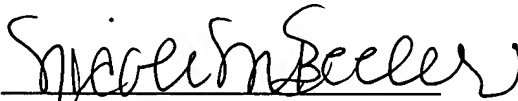
Rejection of Claims 1-11, 13 and 16 under Obviousness-type Double Patenting

The Examiner provisionally rejected Claims 1-11, 13 and 16 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over Claims 1, 2, 7 and 12-14 of co-pending Application No. 10/915,743. Additionally, the Examiner provisionally rejected Claims 1-10 and 16 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over Claims 1, 2, 6 and 7 of co-pending Application No. 10/559,857, Claims 1, 2, 7, 14 and 12 of co-pending Application No. 10/567,676, Claims 1, 5, 10 and 11 of co-pending Application No. 10/916,096, and Claims 1, 2 and 6 of co-pending Application No. 10/568, 000.

As these rejections are provisional rejections based on pending applications which are still undergoing prosecution and wherein no allowable subject matter has yet been identified, Applicants respectfully request that this rejection be held in abeyance.

If a telephonic communication with the Applicants' representative will advance the prosecution of the instant application, please telephone the representative indicated below. Applicants believe no additional fees are due but the Commissioner is authorized to charge any fees required in connection with this amendment to Merck Deposit Account No. 13-2755.

Respectfully submitted,

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Date: July 24, 2007

Attachment – Iwasawa article

A Highly Efficient Synthesis of (–)-PI-091 Construction of the 4-Alkoxy-2-butene-4-lactam Skeleton from Fischer-Type Carbene Complexes, Alkynyllithiums, and Tosyl Isocyanate

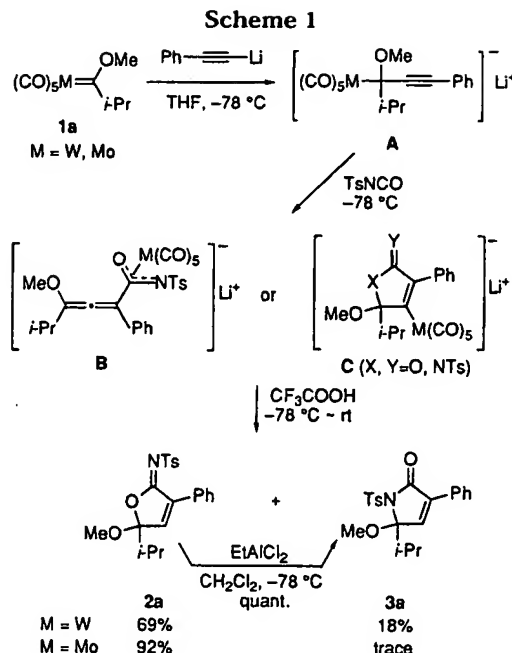
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Received January 14, 1997

The 4-alkoxy-2-butene-4-lactam skeleton has attracted much attention because it forms the basic structure of several pharmacologically promising natural products such as PI-091,¹ epolactaene,² and so on.³ However, the construction of this carbon framework with appropriate substituents is not necessarily easy, and multiple transformations are usually required.⁴ In a previous paper, we reported that a new type of propargyl metallic species is generated by the addition of alkynyllithiums to Fischer-type carbene complexes and that these propargyl metallic species react with various carbon electrophiles such as aldehydes, sulfonylimines, and carbon dioxide to give furans, pyrroles, and 5-alkoxybutenolides, respectively.⁵ We considered employing an isocyanate, a nitrogen analogue of carbon dioxide, as an electrophile with the expectation that the 4-alkoxy-2-butene-4-lactam skeleton bearing various substituents could be constructed in a single step. In this paper is described a successful realization of this approach and its application to a concise enantioselective synthesis of (–)-PI-091.

Examination of several isocyanates revealed that tosyl isocyanate⁶ reacts with the propargyl metallic species generated from Fischer-type carbene complexes and alkynyllithiums. Thus, propargyl metallic species A, generated by the addition of (phenylethynyl)lithium to isopropylcarbene complex 1a (M = W) at –78 °C, was reacted with tosyl isocyanate at this temperature overnight to give either an allenyl intermediate B or a [3 + 2] cycloaddition intermediate C.^{6,7} The reaction mixture was then treated with trifluoroacetic acid to promote either cyclization (in the case of B) or protonation (in the case of C), giving a mixture of an O-cyclized product 2a and an N-cyclized product 3a in 69 and 18% yield, respectively (Scheme 1). When the corresponding mo-



lybdenum complex 1a (M = Mo) was used for this reaction, the O-cyclized product 2a was obtained in 92% yield, and only a trace amount of the N-cyclized product 3a was produced.⁸ Furthermore, it was found that the purified 2a was quantitatively isomerized to 3a by treatment with ethylaluminum dichloride in dichloromethane at –78 °C. To obtain the N-cyclized product 3a selectively, the crude product of the addition reaction with tosyl isocyanate was directly treated with ethylaluminum dichloride in dichloromethane to give 3a in 79% overall yield based on the carbene complex 1a (M = Mo).

We then examined the generality of this reaction. As summarized in Table 1, N-cyclized product 3 was obtained in good yields in every case.⁹ Thus, this reaction is a highly efficient method for the construction of the 4-alkoxy-2-butene-4-lactam skeleton with various substituents from carbene complexes, alkynyllithiums, and tosyl isocyanate.

We next applied this reaction to the enantioselective synthesis of (–)-PI-091. PI-091 was isolated in 1990 by the research group at Taisho Pharmaceutical Co. from

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(1) Kawashima, A.; Yoshimura, Y.; Sakai, N.; Kamigoori, K.; Mizutani, T.; Omura, S. *Jpn. Kokai Tokkyo Koho JP 02 62859* [90 62-859] (C1.C07D207/38), 02 Mar 1990, Appl. 88/215,393,30 Aug 1988; *Chem Abstr.* 1990, 113, 113856d.

(2) Kakeya, H.; Takahashi, I.; Okada, G.; Isono, K.; Okada, H. *J. Antibiot.* 1995, 48, 733.

(3) (a) Lam, Y. K. T.; Hensens, O. D.; Ransom, R.; Giacobbe, R. A.; Polishook, J.; Zink, D. *Tetrahedron* 1996, 52, 1481. (b) Singh, S. B.; Goetz, M. A.; Jones, E. T.; Bills, G. F.; Giacobbe, R. A.; Herranz, L.; Stevens-Miles, S.; Williams, D. L., Jr. *J. Org. Chem.* 1995, 60, 7040.

(4) Dittami, J. P.; Xu, F.; Qi, F.; Martin, M. W.; Bordner, J.; Decosta, D. L.; Kiplinger, J.; Reiche, P.; Ware, R. *Tetrahedron Lett.* 1995, 36, 4201. References are cited therein.

(5) Iwasawa, N.; Maeyama, K.; Saitou, M. *J. Am. Chem. Soc.* 1997, 119, 1486.

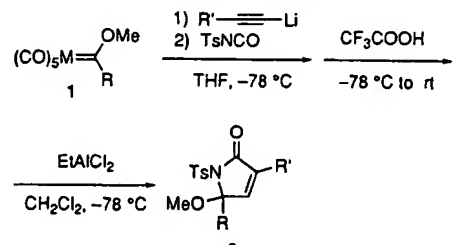
(6) For examples of the reactions of transition metal propargyl metallic species with tosyl isocyanate: (a) Giering, W. P.; Raghu, S.; Rosenblum, M.; Cutler, A.; Ehntholt, D.; Fish, R. W. *J. Am. Chem. Soc.* 1972, 94, 8251. (b) Raghu, S.; Rosenblum, M. *J. Am. Chem. Soc.* 1973, 95, 3060. (c) Bell, P. B.; Wojcicki, A. *Inorg. Chem.* 1981, 20, 1585. (d) Shuchart, C. E.; Willis, R. R.; Wojcicki, A. *J. Organomet. Chem.* 1992, 424, 185. (e) Welker, M. E. *Chem. Rev.* 1992, 92, 97.

(7) We have not yet succeeded in isolating this intermediate.

(8) No isomerization of O-cyclized product 2a to N-cyclized product 3a was observed under these conditions (trifluoroacetic acid in THF at rt).

(9) The reaction was carried out as follows: To a THF solution (5 mL) of an alkyne (0.90–1.2 mmol) was added dropwise a 1.56 M hexane solution (0.40–0.53 mL, 0.62–0.83 mmol) of *n*-butyllithium at –78 °C. After the mixture was stirred for 30 min at this temperature, a THF solution (2 mL) of a tungsten or a molybdenum carbene complex (0.30 mmol) was slowly added. After the mixture was stirred for 1 h at –78 °C, a THF solution (4 mL) of tosyl isocyanate (2.0 mmol) was added and the mixture was stirred overnight at –78 °C. Trifluoroacetic acid (0.50 mL) was added at –78 °C, and the mixture was warmed to rt. After the mixture was stirred overnight at rt, triethylamine (1.0 mL) was added at 0 °C and then pH 7 phosphate buffer was added. The organic layer was extracted three times with ethyl acetate, and the combined extracts were dried over MgSO₄. After removal of the solvent, the residue was dissolved in 10 mL of CH₂Cl₂ and a 1.0 M hexane solution of ethylaluminum dichloride (2.0 mL, 2 mmol) was added dropwise at –78 °C. After the mixture was stirred at this temperature for 3 h, 10% aqueous Rochelle salt solution was added carefully to the reaction mixture. The aqueous layer was extracted three times with ethyl acetate, and the combined extracts were dried over MgSO₄. After removal of the solvent, the residue was purified using preparative TLC (hexane:ethyl acetate = 6:4), yielding the corresponding N-cyclized product 3.

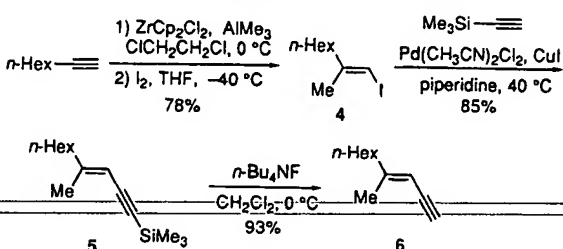
Table 1. Preparation of 4-Methoxy-2-butene-4-lactams



R	R'	M	yield of 3 (%)
<i>i</i> -Pr	Ph	Mo ^a	79 (3a)
<i>i</i> -Pr	<i>n</i> -Hex	Mo ^a	83
Ph	Ph	W	80
Ph	<i>n</i> -Hex	W	87

^a The molybdenum complex gave slightly better yield than the corresponding tungsten complex.

Scheme 2



Paecilomyces sp. F-3430 and exhibits modest arachidonic acid-induced platelet aggregation-inhibitory activity.¹ PI-091 contains the 4-alkoxy-2-butene-4-lactam skeleton and was isolated as a 1:1 diastereomeric mixture at the *N,O*-acetal carbon. Tadano et al. have already reported the first total synthesis of PI-091 starting from D-glucose.¹⁰

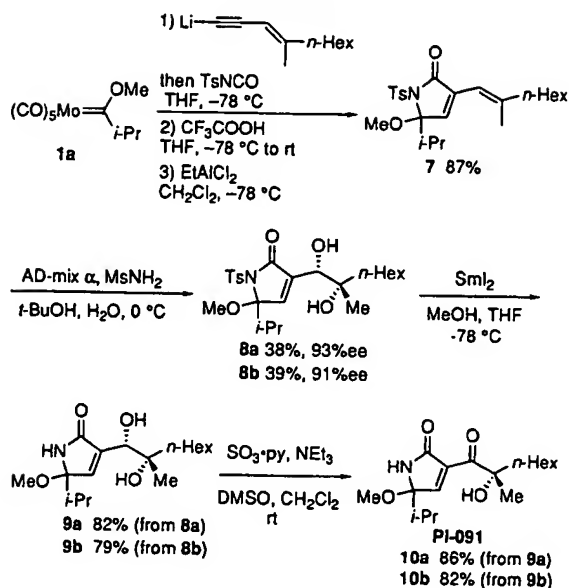
It was expected that the basic structure of PI-091 could be synthesized from the isopropyl carbene complex **1a**, (*E*)-4-methyl-3-decen-1-yne (**6**), and tosyl isocyanate by using our procedure.

The requisite enyne **6** was prepared in a straightforward manner as shown in Scheme 2. Methylalumination of 1-octyne was carried out employing trimethylaluminum and zirconocene dichloride, and the resulting alkenylaluminum species was treated with iodine to give an alkenyliodide **4** in 78% yield.¹¹ It was then coupled with (trimethylsilyl)acetylene by using Pd(CH₃CN)₂Cl₂ and CuI in piperidine¹² to give **5**, which was desilylated by tetrabutylammonium fluoride to give the enyne **6** in 79% yield from **4**.

With the enyne **6** in hand, we examined formation of the 4-alkoxy-2-butene-4-lactam. According to the procedure described above, the lithiated enyne **6** was reacted with isopropylcarbene complex **1a** to generate a propargyl metallic species, and then tosyl isocyanate was added. After two successive acid treatments (trifluoroacetic acid and then ethylaluminum dichloride), the expected 4-alkoxy-2-butene-4-lactam **7** was obtained in 87% yield.

Conversion of this intermediate **7** to PI-091 was carried out in a straightforward manner as shown in Scheme 3.

Scheme 3



Regio- and enantioselective dihydroxylation of the side chain olefin was achieved by using AD-mix α¹³ to give a diastereomeric mixture of diols **8a** and **8b**.¹⁴ These two isomers were easily separated by TLC, and the optical purities of **8a** and **8b** were determined to be 93% ee and 91% ee by using chiral shift reagents Eu(hfc)₃ and Pr(hfc)₃, respectively. Although reductive removal of the tosyl group from **8** turned out to be quite troublesome due to facile over-reduction, finally it was found that samarium(II) diiodide in methanol gave about 80% yield of the deprotected product **9**. The final stage of the synthesis was the oxidation of the secondary hydroxyl group, which was carried out in good yield by using SO₃·pyridine in DMSO. The ¹H and ¹³C NMR spectra and optical rotations of the products obtained, **10a** and **10b**, agreed well with those of the natural product.¹⁵

In conclusion, we have developed a facile method for the construction of the 4-alkoxy-2-butene-4-lactam skeleton by the reaction of the propargyl metallic species, generated from Fischer-type carbene complexes and alkynyllithiums, and tosyl isocyanate. Furthermore, a highly efficient total synthesis of PI-091 was achieved by using this method.

Acknowledgment. We are grateful to the Research Laboratories for Applied Biology, Taisho Pharmaceutical Co., Ltd. for donating ¹H and ¹³C NMR spectra of PI-091. This work was financially supported in part by the Fujisawa Foundation and a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture, Japan.

Supporting Information Available: Experimental procedures and spectroscopic data are included for compounds 2–10 (9 pages).

JO9700686

(10) (a) Shiraki, R.; Sumino, A.; Tadano, K.; Ogawa, S. *Tetrahedron Lett.* 1995, 36, 5551. (b) Shiraki, R.; Sumino, A.; Tadano, K.; Ogawa, S. *J. Org. Chem.* 1996, 61, 2845.

(11) Rand, C. L.; Van Horn, D. E.; Moore, M. W.; Negishi, E. *J. Org. Chem.* 1981, 46, 4093.

(12) Takahashi, S.; Kuroyama, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* 1980, 627.

(13) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.; Kwong, H.; Morikawa, K.; Wang, Z.; Xu, D.; Zhang, X. *J. Org. Chem.* 1992, 57, 2768.

(14) Diastereomers arise from configuration at the *N,O*-acetal carbon. The relative stereochemistries of **8a** and **8b** were not determined.

(15) Although natural PI-091 is a mixture of diastereomers, both **10a** and **10b** show nearly the same optical rotation as the natural product.